

**Meeting of the States Parties to the Convention
on the Prohibition of the Development,
Production and Stockpiling of Bacteriological
(Biological) and Toxin Weapons and on Their
Destruction**

18 July 2018

English only

2018 Meeting
Geneva, 4-7 December 2018

**Meeting of Experts on Review of developments in the field
of science and technology related to the Convention**
Geneva, 9-10 August 2018

Item 6 of the provisional agenda

**Development of a voluntary model code of conduct for biological scientists and
all relevant personnel, and biosecurity education, by drawing on the work already
done on this issue in the context of the Convention, adaptable to national requirements**

**Germany's best practice in handling (bio)security-
relevant research: Self-governance organized by
the German National Academy of Sciences
Leopoldina and the German Research Foundation
(DFG)**

Submitted by Germany

1. Scientific research plays a fundamental role in ensuring progress. Scientific freedom, which is enshrined in the German Basic Law, is a fundamental requirement in this respect. Yet free research is also associated with risks which result primarily from the danger of useful research findings being misused, for example as weapons of war and means of criminal or terrorist activities.
2. In the opinion of the German National Academy of Sciences Leopoldina and the German Research Foundation (DFG), legal provisions offer only a very limited means of controlling the opportunities and risks associated with free research. Research methods and content are constantly changing and research findings, as well as their future application, tend to be almost impossible to predict. The Leopoldina and the DFG continuously work to ensure that ethical principles and mechanisms for the responsible handling of free research and research risks are developed in science. As a response to the gain-of-function debate, in 2013, the DFG updated its "Code of Conduct: Working with Highly Pathogenic Microorganisms and Toxins" (see Annex) which is still valid today with the new scientific methods and opportunities of genome editing and of synthetic biology.
3. Moreover, in 2014, the DFG and Leopoldina published a set of general guidelines on handling security-relevant scientific research under the title "Scientific Freedom and

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Scientific Responsibility – Recommendations for Handling Security-Relevant Research”¹

This document places great importance on instruments of self-governance within the scientific community. The advantage of self-governance lies in researchers' high level of familiarity with the given subject and the fact that it allows for a flexible response. The recommendations are intended as an aid for researchers as well as a blueprint for research institutions implementing the corresponding regulations. They are aimed primarily at the government-funded research sector. However, their principles can certainly also be applied in the private sector.

4. In order to support German research institutions in the sustainable implementation of the Recommendations for Handling Security-Relevant Research, Leopoldina and DFG established the Joint Committee on the Handling of Security-Relevant Research. The Joint Committee consists of 12 scientific experts in relevant disciplines – from natural and life sciences to IT science, engineering, ethics and jurisprudence. The two chairpersons of the Joint Committee are a named representative of the Leopoldina Presidium and the Vice-President of the DFG.

5. The Joint Committee stays abreast of the progress in enacting the Recommendation on Handling Security-Relevant Research through monitoring and provides support to the research institutes for the implementation of the recommendations. Furthermore, the Joint Committee serves as a contact point for questions and a platform for the bundled exchange of information. Therefore, already more than 120 contact persons for handling security-relevant research have registered on the Joint Committee's website.² If it is not possible for an adequate decision about a particular case to be made locally, the Leopoldina may appoint ad-hoc working groups that, in close cooperation with the Joint Committee, can make a risk-benefit assessment of the research project in question.

6. In line with recommendations of DFG and Leopoldina, already more than 70 local committees for ethics in security-relevant research have been established throughout Germany. These committees enable the individual institutes to properly and responsibly deal with troubling issues arising from specific research projects and to decide themselves how to continue. By supporting the responsible self-governance of the scientific community, these mostly advisory bodies may also act as a means to strengthen compliance with the BWTC.

¹ Available at: www.leopoldina.org/uploads/tx_leopublication/2014_06_DFG-Leopoldina_Scientific_Freedom_Responsibility_EN.pdf

² Available at: www.leopoldina.org/en/about-us/cooperations/joint-committee-dual-use/list-of-committees

Annex

Code of Conduct: Working with Highly Pathogenic Microorganisms and Toxins

German Research Foundation (DFG) Senate Commission on Genetic Research (13 March 2013)

1. In recent years there has been rapid development in research in the field of infections, immunity and pathogenicity factors. The use of highly pathogenic microorganisms in research has yielded important scientific findings. The function of bacterial toxins, the entry and spread of highly pathogenic viruses in host cells and the relationship between cellular and humoral immunity and highly pathogenic microbes are all examples of areas of research that offer important potential for both basic research and the development of new diagnostic methods, treatments and vaccines.

2. However, the use of highly pathogenic microorganisms and toxins comes with the risk that research findings could be used to develop biological weapons. This is referred to as the 'dual use problem', and it is not limited to research involving highly pathogenic microorganisms and toxins. Examples of findings which are affected by this problem can also be found in other fields, such as materials science, computer science and even the social sciences. There exists a consensus that public safety should be considered the highest priority. However, we must also consider the benefits to human health that can be achieved through research with pathogenic organisms, as well as freedom of research and freedom of publication.

3. The Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) has discussed the dual use problem on many occasions in its statutory bodies. The DFG wants to provide researchers with a code of conduct which addresses the problems of working with highly pathogenic microorganisms and toxins and responds to the specific situation in Germany. The DFG has therefore drawn up the following recommendations for researchers working with highly pathogenic microorganisms and toxins:

(a) The DFG agrees with the decision of the National Research Council of the National Academies in the USA, which believes the following experiments to be particularly relevant to the dual use problem:

- Efforts to increase the virulence of pathogenic microorganisms or to convert apathogenic microbes into pathogenic microbes
- Experiments to induce resistance to effective antibiotics and antiviral substances
- Experiments to increase the transmissibility of pathogens
- Experiments to modify the host spectrum and stability of pathogens
- Efforts to avoid methods of diagnosis and detection
- Efforts to disclose the ineffectiveness of vaccines
- Experiments to make biological agents or toxins more suitable for use as weapons (weaponisation)

(b) The DFG believes it is necessary to carry out research work with pathogenic microorganisms and toxins. This is the only way in which we can develop strategies to combat dangerous pathogens and protect the population against infections. In addition,

many findings in basic research have been the result of work involving highly pathogenic microorganisms and toxins. The DFG therefore believes that as few restrictions as possible should be imposed on research involving pathogenic microorganisms.

(c) However, the DFG also promotes a responsible approach to work of this type. It expects researchers to evaluate their experiments at the planning stage and before starting work with regard to a potential dual use problem and to document this evaluation process in the laboratory records. This applies to the experiments themselves and to planned publications.

(d) The DFG will continue to fund research which addresses problems relating to highly pathogenic microorganisms and toxins. However, principal investigators should address an existing or potential dual use problem in their proposals. Reviewers are requested to assess the information provided by applicants and make a recommendation to the review boards.

(e) In the case of proposals where the dual use problem is applicable, the review boards will if necessary following preparation in an ad hoc working group carefully examine the proposals and, if appropriate, make suggestions as to how the proposed work should be carried out. If necessary, the responsible Senate Commission and/or the Senate may be involved in the process.

(f) The DFG does not believe that preventing the publication of sensitive findings is an effective way of minimising misuse. It believes that researchers must be allowed to continue publishing data relating to highly pathogenic microorganisms and toxins in peerreviewed journals. The publication of research data is a central requirement for scholarly self-evaluation. Only known dangers can be countered. The specific publication guidelines of the journals in question should always be observed.

(g) The DFG believes it is necessary to continue funding international cooperation, academic exchanges and the sharing of data, materials and methods in relation to research on pathogenic microorganisms and toxins. The appropriate national and international laws and guidelines must of course be observed.

(h) The DFG suggests that universities and non-university institutions should regularly hold seminars and other events for students, doctoral researchers and postdoctoral researchers on the subject of working with highly pathogenic microorganisms and toxins. The annual briefings required by the Genetic Engineering Act also provide an opportunity to raise awareness of the dual use problem. Research Training Groups, graduate schools, Collaborative Research Centres, research centres and clusters of excellence in relevant disciplines also provide suitable opportunities.

(i) The DFG advocates the continued development of best practice in connection with highly pathogenic microorganisms and toxins and the ongoing adaptation of the scientific framework. Findings should be shared with other organisations within Germany and abroad, for example the Medical Research Council (MRC) and the Wellcome Trust in the UK and the American Society for Microbiology (ASM). Relevant specialist associations and scientific academies could also make important contributions to this process.

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**Meeting of Experts on Review of developments in the field
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Geneva, 9-10 August 2018
Item 7 of the provisional agenda
**Genome editing, taking into consideration, as appropriate,
the issues identified above**

**Technical Working Paper on Genome Editing and
Other Scientific and Technological Developments
of Relevance to the Convention**

Submitted by Switzerland

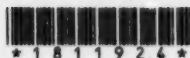
I. Introduction

1. The Biological and Toxin Weapons Convention (BTWC) faces a significant acceleration of relevant scientific and technological developments. This may put into question previous certainties and achievements. As a consequence, there is a vital need to identify relevant developments, consider their implications, and pinpoint any necessary individual or collective action to address possible challenges. A meaningful technical exchange among experts at the MX2 – Review of Developments in the Field of Science and Technology Related to the Convention – will be a much needed first step in that regard. To facilitate an interactive technical debate, this Working Paper puts forward non-exhaustive considerations of scientific and technological developments Switzerland deems relevant for expert discussions in the framework of MX2. It focuses on the specific topic for 2018, i.e. genome editing, paying particular attention to advances in CRISPR technology[1]. It also covers the issue of nucleic acid origami[2].

II. Genome Editing

2. Genome editing is not a new field of active research and existed long before today's often cited CRISPR technology. Even CRISPR, which is an abbreviation for 'clustered regularly interspaced short palindromic repeat', was already described in the early

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1990s[1]. It took, however, another decade to recognize that these particular regions in bacterial DNA do in fact contain short pieces of foreign genetic material. A 2005 report[3] made the link to a never before described adaptive bacterial immune system, i.e. an immune system that is in a position to adapt to new challenges it is faced with. In 2012, another report[4] elaborated on the mechanistic details of this immunity that relies on Cas (CRISPR-associated) proteins. This study also coined the concept of CRISPR-Cas9 as a tool for making edits to a genome. Shortly thereafter, further studies[5,6] showed the vast array of potential applications of CRISPR technology that allows to edit genomes in a way that significantly outperforms existing tools in terms of simplicity, speed and costs.

3. Since then, CRISPR technology has spread across the globe and is being applied in an ever growing number of fields, including synthetic biology, disease modelling, and in therapeutic approaches at the genetic level. A myriad of reports in the scientific literature have been published in recent years, among other issues on the correction of genetic mutations in viable human embryos[7], or the application of so called 'gene drives' to alter the genome of an entire mosquito population at exponentially faster rates than Mendelian inheritance would suggest[8]. These also gave rise to concerns in terms of safety and ethics[9].

4. Not preempting any future groundbreaking discoveries related to the still nascent CRISPR technology, it may likely boil down to the same well-trodden path of previous novel technologies: In various settings, its applicability proves more difficult than anticipated and solutions to any encountered obstacles demand an ever more complex degree of sophistication. For instance, longer-term studies of 'gene drives' have uncovered the emergence of resistance[10,11] that will add much complexity to any future attempts aimed at making it a useful tool in practical terms. Furthermore, a proof of concept study on the potential applicability of CRISPR technology in gene therapy[12] highlighted problems with efficiency of delivery and so called 'off-target effects'. Since improvements in these areas are of utmost importance for future success, several reports have been published recently on related advances: increasing delivery rates by virus-mediation[13], lowering off-target effects by increasing the fidelity of Cas9[14], and the description of an increasing spectrum of alternate proteins[15] such as Cpf1 and Cas13a.

5. Despite such promising advances that try to level out encountered difficulties, the root cause of some of the problems, such as the efficiency of CRISPR technology in particular cell types, may be more intricate than anticipated. For instance, results of a mechanistic analysis in human pluripotent cells demonstrated that reduced efficiencies of CRISPR technology seem to be based on inhibition by p53[16,17] – short for cellular tumor antigen p53 –, a protein sometimes labelled as 'guardian of the genome' alluding to its protective function as a tumor suppressor by preventing mutations and thus preserving genome stability. In other words, it appears that CRISPR technology works in cells that may have inactive or corrupt copies of p53. This could lead to selection of cells in which CRISPR technology works but at the cost of increased genome instability which, in turn, could lead to cancer[18].

6. In yet another area of active research, CRISPR technology, on the one hand, was commented as potentially obfuscating current microbial analysis approaches of value to forensics. This challenge emanates from the mode of action of CRISPR technology that hardly leaves any 'traces', unlike any former techniques would do. Hence, CRISPR technology inevitably decreases confidence in differentiation between genetic engineering and conventional mutagenesis[9], and likely between naturally occurring and man-made alterations. CRISPR technology may, on the other hand, open up new avenues for rapid, inexpensive, sensitive, and potentially field deployable nucleic acid detection through CRISPR-Cas13a[19].

III. Other Scientific and Technological Developments

7. The ability to fold nucleic acid strands into designed two- or three-dimensional shapes and structures, sometimes with a 'built-in' ability to perform specific mechanical functions and movements, exists already for many years[2]. Until recently, such nucleic acid origami encompassed a cumbersome design process through the creation of purified DNA strands. This niche technology suffered from an important bottleneck caused by a laborious and expensive nucleic acid synthesis, which prevented any serious up-scaling ambitions. A first significant step was achieved by either tapping into naturally occurring DNA[20], especially from abundantly available viruses, serving as 'scaffold', or by using a system of nucleic acid 'bricks'[21,22] for the customized building of shapes and structures. Less than a year ago, scientific reports demonstrated that biotechnological mass production was possible for programmable self-assembly of ever larger structures[23,24,25,26].

8. With the increased accessibility of nucleic acid origami, structures able to perform specific mechanical functions and movements may gain renewed attention from the scientific community and other stakeholders. Especially systems designed to carry molecular payloads[27,28] may now become more relevant for discussions on advances in science and technology within the BTWC.

IV. Conclusions and Recommendations

9. CRISPR technology can reasonably be expected to surprise us with new twists and turns impossible to predict. This is likely also true for many other areas, including the above discussed nucleic acid origami, but also for synthetic biology or the neurosciences. In this context, it will be important to keep track of scientific and technological advances, and their potential bearings on the Convention. At the upcoming MX2, we should hold a technical discussion on genome editing technologies, and especially CRISPR technology, to then take the next step towards an assessment of their implications for the Convention by putting them into the broader context of the 'new era of biology'. In doing so, we should broaden our traditional focus of 'pathogens causing disease' to the wider prospects and implications that developments in the biosciences as a whole may have. Furthermore, technical discussions should also take into account any intangible aspects (e.g. 'tacit knowledge') of advances in science and technology, which may significantly shift initial perceptions about benefits and risks. All of this will allow for a holistic and more realistic understanding of the benefits and risks to the Convention.

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Genome editing, taking into consideration, as appropriate,
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**Review of Developments in the Field of Science
and Technology Related to the Convention -
Genome editing**

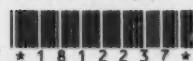
Submitted by Australia

I. Overview

1. The rapid advances in genome engineering technology, in particular, the emergence of clustered, regularly interspaced, short palindromic repeat (CRISPR) has revolutionised human, animal, plant and ecosystem health. The CRISPR/Cas9 system is a site-directed nuclease that can be used for altering genetic loci through insertions, deletions and point mutations in virtually any organism, creating changes that fall into different categories of genome engineering. The insertion of foreign DNA generates genetically modified organisms (GMOs), whereas site-directed mutations including deletions and small base pair changes are classified as gene editing. Gene editing outcomes can be generated with a site-directed nuclease alone or in combination with a DNA repair template. Rapid advances over recent years have resulted in improved efficiency, relatively high precision and low cost, making this technology now a mainstream method, accessible to academic, government or industry laboratories and potentially even civilian run laboratories. These characteristics have also led to some concern over how quickly applications for beneficial or harmful uses will be developed and spread.

2. BWC MX2 on "Review of Developments in the Field of Science and Technology Related to the Convention" offers the opportunity to discuss emerging technologies and consider potential risks and benefits relevant to the Convention. The current paper provides an overview of the capabilities and regulations associated with this technology in Australia and the implications for Australia and the Indo-Pacific region. Increased transparency and sharing of information on the experiences of States Parties in managing the risks associated with gene editing, including through regulation, is a useful way to strengthen the BWC and keep it relevant to contemporary challenges.

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II. Accessibility of gene editing: what are the risks and rewards?

3. Methods for genome editing are readily available in scientific papers and on the internet. Additionally, CRISPR/Cas9 kits can be ordered online relatively cheaply by anyone, regardless of their training or expertise. This ready availability has accelerated progress and allowed the technology to be used across a variety of applications. The use of genome engineering to make disease vectors less effective at carrying pathogens such as malaria, developing novel human therapeutics, improving disease resilience of host species to pathogens, and for controlling invasive species are among the benefits promised by this technology.

4. The availability of tools and information to edit the genomes of many different organisms ranging from cattle⁽¹⁾ to vaccinia virus⁽²⁾ has also led to concerns over misuse of such information and its potential as a biosecurity threat. In the past inadvertent discoveries have also led to the dissemination of information that could be used for harm. One example is the unintentional development of a lethal mousepox virus using standard genetic modification techniques to insert the gene for interleukin 4 (IL4) into the mousepox viral genome, an insertion which was intended to be used to induce infertility in mice. Instead, the altered virus was lethal in naturally resistant mice, and mice that had been vaccinated against mousepox. When the authors published their findings, critics were concerned that this information could be used by would-be terrorists as a new way of making biological weapons^(3,4). Beyond micro-organisms, there is also the possibility of engineering vectors such as mosquitoes that spread pathogens such as Zika or Dengue viruses more effectively.

5. While risks of misuse of this powerful new technology exist, it should be noted that although new site-directed nuclease such as CRISPR/Cas9 are accessible and easier to use than former methods, to use any genome engineering tools in conjunction with microorganisms one must still have access to the live microorganisms and the capacity to grow those microorganisms in culture and deliver the genome engineering tools to those cells. In multicellular eukaryotic organisms these tools are even harder to use on an organismal level as one must have access to either gametes, stem cells, or embryos to make germ line transmissible changes to the genome. Thus, to effectively undertake a gene editing project in any organism would require access to that organism, training in laboratory techniques, and access to basic laboratory equipment.

III. Regulations governing gene editing technology in Australia

6. Australia's governing body that regulates all genetically modified organisms, the Office of Gene Technology and Research (OGTR) within the Australian Government Department of Health is responsible for administering the Gene Technology Act 2000 and corresponding state and territory laws. The OGTR oversees all work involving gene technology performed in Australia, including the development of policy guidelines in relation to genetically modified organisms. In the 2001 Explanatory Statement to the Gene Technology Regulations, the scope of gene technology as defined by the scheme states that any process that involves moving and rearranging genes between species is considered gene technology and results in GMOs, whereas techniques which mimic natural processes and work through natural mechanisms do not result in GMOs. As such, organisms resulting from technologies such as chemical and radiation induced mutagenesis are not considered to be GMOs for the purposes of the legislation because the process mimics natural mutation processes⁽⁵⁾.

7. The emergence of new tools including site-directed nucleases such as CRISPR/Cas9 triggered a technical review of the gene technology regulations in Australia which began in 2016⁽⁶⁾. In early 2018, the OGTR set forth recommendations based on the technical review proposing that organisms modified using site-directed nucleases without DNA templates to

guide genome repair should not be regulated as GMOs, as the site-directed nucleases only cleave DNA and all resulting mutations at the cleavage site are generated through natural cellular processes. Any organisms generated using site-directed nucleases in conjunction with DNA templates to direct repair of the DNA cleavage will be regulated, as the use of DNA repair templates constitutes gene technology⁽⁷⁾.

8. While organisms made using only site-directed nucleases would not be regulated under this proposal by the OGTR, there are currently no domestic sources of CRISPR/Cas9 plasmids, mRNA, or protein, thus all non-laboratory organisms (as classified by the Australian Department of Agriculture and Water Resources)⁽⁸⁾ made with these reagents would still fall under quarantine regulations regarding the *in vivo* use of imported biologics (importing biological products for use in non-laboratory animals). As many other countries are also grappling with how they will regulate organisms made using site-directed nucleases, it will be useful to hear the experiences of other States Parties during the MX, as such dialogue helps us to share best practice, and avoid mistakes.

9. Other jurisdictions are also currently deciding how they will regulate organisms made using site-directed nucleases. Overall, the international regulatory landscape surrounding site-directed nucleases like CRISPR/Cas9 remains very fragmented, with a significant focus on the regulation of commercially relevant agricultural species, human therapeutics, and microorganisms used in industrial processes. As is the case with more traditional techniques used for genetic modification, the burden of closely monitoring the use of these technologies in harmful microorganisms falls to separate institutions, be they scientific, medical, academic or government. Institutions have an ethical and legal responsibility to ensure that biosecurity standards are maintained for all work taking place at the institution and for instilling a positive and transparent culture in the workplace.

10. All organisations in Australia undertaking dealings with GMOs undergo accreditation to assess whether they have the resources and the internal processes in place to enable effective oversight of work with GMOs. This includes access to an appropriately constituted Institutional Biosafety Committee which provides on-site scrutiny of low-risk contained dealings through independent assessment to ensure compliance with legislative requirements. All staff undertaking work with GMOs are also required to undertake training to ensure they are aware of the regulations and requirements. Despite these requirements, there will always be the risk that staff members who have access to harmful microorganisms and the expertise to use genome engineering techniques on them may use this material and their expertise for harmful purposes, even if these activities are illegal. Strong institutional oversight of projects, restricted access to harmful microorganisms, and clear reporting mechanisms for documenting the possible risks associated with these types of projects are ways that institutions can prevent either unintentional or malicious misuse by staff of the materials and expertise they have been entrusted with.

IV. Facilities for high containment and Resources for Capability building

11. The Australian Animal Health Laboratory in Geelong, Victoria is the largest high containment lab in the Southern hemisphere with laboratory and animal capacity to work with pathogens up to the highest level of containment, biosecurity level 4 (BSL4). The lab also has significant expertise in genome engineering and diagnostics. To this end, genome engineering is being used for a variety of applications, including projects involving editing the engineering of animals to confer improved disease resistance, control invasive species, and in mosquitoes to decrease disease transmission.

12. Although the high containment lab was originally built to contain dangerous pathogens, it also provides the opportunity to contain genetically modified or gene edited

organisms, including animals, microorganisms and insect vectors of disease without the risk of accidental release. In the event of a natural incursion or intentional release of a harmful agent, this laboratory is well placed in the Indo-Pacific region to perform diagnostics and coordinate a response plan. In addition, this laboratory is an ideal place to test potential therapeutics against novel pathogens using animal models at high biocontainment.

13. In addition to laboratory capacity in Australia, training and capacity building in other countries in the Indo-Pacific region is critical for disease preparedness against outbreaks due to naturally occurring and intentionally released organisms. To this end, the Australian Government launched the A\$300 million, five year Indo-Pacific Health Security Initiative on 8 October, 2017. The program is focused on building capacity in emerging infectious diseases in the Indo-Pacific region, including supporting action at the country or subregional level to strengthen regional capacity to prevent, detect and respond to emerging and re-emerging infectious disease threats with the potential to cause social and economic harms on a national, regional or global scale. This will include training of scientists and lab workers in biosafety, biosecurity and laboratory diagnostics. This capability has the potential to extend to the ability to respond to and detect a threat posed by a deliberately released, modified microorganism.

V. Synthetic biology – the next biothreat?

14. Synthetic biology is the ability to design and build artificial biological systems for research, engineering and medical applications⁽⁹⁾. Beyond the risks posed by genome editing, the issues in the future may have more to do with the synthesis of new pathogens rather than editing known pathogens to make them more virulent. Even if the agent is restricted, the DNA is not. The most likely applications for synthetic biology could involve recreation of known pathogens such as the highly virulent 1918 Spanish flu whose sequence is publicly available⁽¹⁰⁾. Another example which has raised recent concern is the publication of a method to reconstruct horsepox virus by gene synthesis⁽¹¹⁾. Given the close relationship between horsepox and smallpox virus, implications for the transfer of the techniques used for horsepox have clear implications for public health and biosecurity if they were applied to the synthesis of the smallpox virus.

15. A number of companies provide DNA synthesis services, allowing a client to order synthesised DNA material as short oligonucleotides of less than 100 nucleotides or DNA sequences of between 200-3000 nucleotides in length. Although there are a number of ways of producing a synthetic viral genome using either short oligonucleotides or longer DNA sequences, the technical challenges associated with creating a functional genome are considerable. As with genome engineering, the extensive knowledge and technical expertise required for synthetic biology applications may prevent its misuse, at least in the short term. Although the risk remains small at this stage, the consequences of the misuse of synthetic biology are considerable. Managing the risks by careful regulation of materials, including the distribution of synthetic DNA and methods for generating novel organisms will be assisted by international consideration and cooperation in the BWC framework. The applications of synthetic biology as they relate to the creation of biological weapons is an important issue that should be considered by the Biological Weapons Convention as a potential topic for the 2019 meeting.

VI. Conclusions

16. The rapid advancement of genome engineering and synthetic biology have generated considerable concern that their misuse could create a new generation of biological weapons. The technical expertise required for genome engineering places it beyond the reach of most terrorist groups. However, regulation of GMOs, quarantined biologics, and harmful

microorganisms, by Australian Government agencies such as the Office of the Gene Technology Regulator and Department of Agriculture and Water Resources play an important part in ensuring the safe use of this technology. Institutions, be they scientific, medical, academic or government, also have an important role to play in ensuring that biosecurity is maintained and that employees who have the technical expertise to use genome engineering or synthetic biology and access to biological agents do not use them for harm. Concerns over genome engineering and synthetic biology can also be addressed to some extent by improvements in our capacity to respond to emerging infectious diseases. To this end, Australia's existing capabilities in emerging infectious diseases and the capacity building activities of programs such as Australia's Indo-Pacific Centre for Health Security are important for maintaining and building the capacity to respond to infectious disease outbreaks that occur either naturally or due to intentionally released, modified organisms. Gene editing is a useful, relevant topic for BWC experts to consider, and MX2 will provide an important opportunity to start the discussion. It will be equally valuable to continue the dialogue building on the meeting in August 2018.

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Footnote

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**Meeting of the States Parties to the Convention
on the Prohibition of the Development,
Production and Stockpiling of Bacteriological
(Biological) and Toxin Weapons and on Their
Destruction**

26 July 2018

English only

2018 Meeting
Geneva, 4-7 December 2018

**Meeting of Experts on Review of developments in the field
of science and technology related to the Convention**
Geneva, 9-10 August 2018
Item 7 of the provisional agenda
Genome editing, taking into consideration, as appropriate,
the issues identified above

**Genome editing: addressing implications for the
Biological and Toxin Weapons Convention**

**Submitted by the United Kingdom of Great Britain and
Northern Ireland**

I. Introduction

1. Recent developments in genome editing were introduced during the 2012 to 2015 Intersessional Programme Standing Agenda Item on review of developments in the field of science and technology related to the Convention. In particular, advances in CRISPR-based technology, derived from the natural defence mechanisms of bacteria, gave it potential as a powerful genomic engineering tool also applicable in more complex organisms, including plants, insects, animals and humans. Its increasing affordability, accessibility, precision and rapidity enhanced this potential. However, the rapid emergence and advancement of this field meant that the implications for the Convention, particularly the security implications, were uncertain and difficult to predict.

2. Detailed technical descriptions of genome editing have been provided in presentations and Working Papers at previous BTWC meetings¹ and will also be covered in contributions to this MX2. This Working Paper focusses instead on the potential

¹ For example: Presentation by Switzerland to 2015 BTWC Meeting of Experts:
[https://www.unog.ch/80256EDD006B8954/\(httpAssets\)/A60F7B2106175E24C1257E9F0065DDEF/\\$file/Swiss_presentation_BWC_MX_2015_S&T-CRISPR_INC.pdf](https://www.unog.ch/80256EDD006B8954/(httpAssets)/A60F7B2106175E24C1257E9F0065DDEF/$file/Swiss_presentation_BWC_MX_2015_S&T-CRISPR_INC.pdf). New scientific and technological developments relevant to the Convention: Some examples. Submitted by the United States of America (BWC/CONF.VIII/PC/WP.18)

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consequences of advances in this field for the elements specified in the MX2 agenda, which are: enhanced implementation of the Convention; identification of potential benefits and risks; biological risk assessment and management; codes of conduct and biosecurity education. In particular, it aims to identify some topics and questions to stimulate expert discussions in MX2 on the opportunities and challenges emerging, and on the actions that States Parties could consider, individually and collectively, to address them.

II. Potential benefits and risks

3. Genome editing has the potential to provide benefits across an increasing number of areas, including in human health, agriculture and the environment. There could also be beneficial outcomes of relevance to implementation of the Convention, for example, in providing support or assistance in the response to the effects of a violation of the Convention under Article VII, and in development and application of scientific discoveries to the prevention of infectious disease under Article X. CRISPR technology is already being developed to prevent and treat disease in humans, to modify plants to deal with the impacts of climate change and plant pathogens, and to halt the spread of viruses in animal populations. It can also be used to edit germline cells in embryos, introducing genetic changes that will be passed on to future generations and which could have potential in the treatment of genetic disorders. Some specific examples of beneficial genome editing applications given in a recent Royal Society Conference Report² include:

- conferring resistance to porcine reproductive and respiratory disease virus in pigs and to the infectious pancreatic necrosis virus in Atlantic salmon;
- targeted mutagenesis to prevent rice blast disease;³
- creation of improved cellular and animal models of disease to understand disease pathways, identify and validate novel drug targets and test the efficacy of new medicines;
- targeting of the genes involved in the symbiosis signalling pathway in barley to help understand their function. This may allow engineering of the pathway for cereal recognition of nitrogen-fixing bacteria, and support the development of nitrogen-fixing cereals, which could play an important role in global food sustainability.

4. The Royal Society Conference Report also addressed the technical, regulatory and ethical challenges associated with the wider adoption of genome editing technology. The broader debate on the socio-economic implications of genome editing has tended to focus on the key ethical, moral and public perception aspects, though there has been some consideration of potential security concerns. In October 2017, the InterAcademy Partnership (IAP) convened an international workshop to assess the security implications of genome editing technology. Its major goal was to enable members of the research, security and policy communities, with wide geographical representation, to discuss potential benefits, security implications associated with intended misuse, and what might be done to prevent or mitigate potential harm.⁴ Discussions focussed on specific applications of

² The CRISPR revolution: changing life: Conference report. Held on 7 March 2018
<https://royalsociety.org/~media/events/2018/03/crispr-revolution-to/TOF-crispr-revolution-report.pdf?la=en-GB>

³ Rice blast disease has been weaponised as a BW agent in the past.

⁴ Assessing the Security Implications of Genome Editing Technology. Report of an international workshop, Herrenhausen, Germany 11-13 October 2017. Convened by the IAP, the European Academies' Sciences Advisory Council (EASAC), the US National Academies of Science,

genome editing, including: human cell editing; editing in agriculture (plants and animals); gene drive applications; and microbial applications. Participants identified beneficial applications similar to those mentioned in the Royal Society report; additional examples included:

- developing gene drives, for example, to control insect vectors of diseases such as malaria;
 - application in transgenic cattle for increased resistance to tuberculosis;
 - development of screens for biological processes or disease;
 - increased understanding of CRISPR functionality in bacteria revealing new opportunities to tackle pathogens, including the major therapeutic goal to avoid development of antimicrobial resistance.
5. Potential security concerns, specifically intentional misuse, were explored taking account of developments in the specific applications. Issues included:
- Human cell editing concerns such as: influencing future human generations; misuse potential for 'off-label' use, for example using a medical product for a muscle disorder for enhancement of military capabilities ('super soldiers'); risk of genome editing viral vectors reaching unintended recipients;
 - Microbial applications have the potential for misuse to construct or alter pathogens suitable for weaponisation⁵; this would be of concern in both human health and agriculture;
 - Gene drive applications could potentially be misused to create threats to human health (e.g., by increasing the transmission of infectious disease by insect vectors) and agriculture (e.g., by increasing insect pests and plant damage).
6. In assessing both potential benefits and risks, it is also important to consider the present and future limitations of the technology and what barriers would have to be overcome to address the challenges. Some examples of limitations include:
- unwanted off target effects which can confound research experiments and present problems for therapeutic applications; development of more specific variants of CRISPR system enzymes could minimise these effects;
 - pre-existing immune responses in humans to proteins in the CRISPR-based technology; this may hinder use to treat disease and could cause significant toxicity to patients; utilisation of alternative enzyme variants may address this;
 - delivery to the target population based on viral-vector systems, which have limitations on size of insert, efficacy and specificity; new approaches being explored include utilisation of gold nanoparticles complexes to improve delivery.

III. Biological risk assessment and management

7. The workshop and its report were intended as the first steps in catalysing and supporting further debate on the security implications of genome editing technology, thus

Engineering and Medicine (NASEM), and the German National Academy of Sciences Leopoldina. <http://www.interacademies.org/Publications/43251.aspx>

⁵ The relevance of the categories of concern identified in the Fink Report was highlighted: National Research Council. 2004. Biotechnology Research in an Age of Terrorism. Washington, DC: The National Academies Press. <https://doi.org/10.17226/10827>

general observations made may now serve as a basis for further assessments. Questions that were debated and which emerged during the workshop's discussions are relevant to our work in MX2, particularly in determining if and what advances in the field might be of concern as a risk to the object and purpose of the Convention, and what strategies might be appropriate to address such risks. Some questions that may help structure our deliberations are set out below.

8. What are we concerned about?

- Which particular developments are most relevant and likely to have impact in the near future?
- What is the feasibility for misuse? Is the technology readily accessible and usable for such activities? What are the limitations?
- What range of activities need to be considered, e.g., direct use of CRISPR technology to cause harmful effects in humans, animals or plants; use of the products of genome editing, such as constructed or altered pathogens, to cause disease; indirect approaches, for example, based on the lack of traceability of CRISPR editing in the product that may challenge microbial forensics?
- Is its application dependent on the simultaneous development of other technologies, such as production and delivery systems? (Applies in both benefit and risk contexts).
- What are the considerations for intangible technology, such as tacit knowledge and the accessibility of the knowledge base for potential misuse?
- Is there anything unique about genome editing in the security context, or can it be considered as an extension of other genetic technologies and addressed in broader considerations of emerging technologies?

9. How should we assess the risks?

- In the absence of broadly accepted norms, how should we assess potential concerns and ensure that benefits and risks are balanced? What regulatory and/or guidance frameworks are available to consider in harmonisation of approaches and best practices? Could we consider a set of guiding principles? Would approaches need to be specific for genome editing/genetic technologies, or could they be wider-based to allow assessment of risks for all relevant emerging technologies?
- Are there relevant case studies on CRISPR-based experiments to utilise in risk assessment? Would case studies from the past or present involving other genetic technologies provide useful lessons? (For example, much-debated cases such as the synthesis of polio virus, construction of the 1918 influenza virus, 'gain of function' avian influenza experiments and construction of the horsepox virus. A recent publication on 'gain of function' analysis of *Yersinia pestis*, the causative agent of plague may also be of interest.⁶)
- Who should be involved in predicting the implications? How do we achieve an optimal balance between scientific, policy, ethical, environmental and security concerns? How do we reflect different national interests and capture a broad range of voices globally to clarify perceived risks and weigh the benefits and risks?

⁶ Palace, S.G. et al. Gain of Function Analysis Reveals Important Virulence Roles for the *Yersinia pestis* Type III Secretion System Effectors YopJ, YopT and YpkA. (2018) Infection and Immunity Accepted Manuscript Posted Online 11 June 2018. Infect. Immun. doi:10.1128/IAI.00318-18.

- Are risk assessments on other aspects, such as safety and ethics, of relevance to implementation of the BTWC? (For example, biosafety assessments may be relevant for implementation of Article IV). How should we interact and keep abreast of discussions and outcomes in other settings?

10. How should we manage the risks?

- What are the primary legal, regulatory and policy measures that could be applied to address and mitigate the potential security risks? Which approaches from the range of governance measures identified (including legislation, regulations, guidelines, standards, funder reviews and oversight, codes of conduct, education, and self-governance) would be appropriate and in what combinations?
- How far can these be harmonised? Is there a risk from conflict between different governance systems (e.g. in different sectors and by other bodies)?
- Are there any technical measures that could be applied to reduce the risks? (For example: safeguarding gene drives to reduce off-target effects and inhibiting spread; increasing efficiency in delivery of viral vectors to ensure specific targeting; development of countermeasures to reverse genome editing or enable detection.)
- Would it be useful to develop guiding principles for balancing the benefits of scientific research with the responsibility to prohibit and prevent the development and acquisition of biological weapons?
- On what aspects should governance measures focus? Generally it was considered that the focus should be on regulating the products of genome editing rather than the technology itself – is this the case for all measures?
- When should decisions on governance be made and at what stage of technology readiness (from initial research through to product) should they be applied? How can we ensure that proportionate and adaptive governance measures are considered?⁷ Are there existing measures that adequately cover, or could be extended to cover, genome editing advances?
- Who needs to be involved in decision-making on governance measures? Who would provide advice to policy makers? What communities have the responsibility to ensure the responsible development of the technology?

IV. Codes of conduct and biosecurity education

11. Codes of conduct and education are amongst the potential measures considered in biological risk management, and would be included in discussions on this element. However, the workshop report includes some relevant feedback from participants. It recognised a need to create a culture of responsibility encompassing researchers, funders, publishers and others, and opportunities to integrate education on security into wider initiatives on responsible research, embedding it in career structures. Ongoing training and education could help ensure that scientists understand the possible dual-use nature of genome editing work. Fostering mentorship was proposed as a core part of developing

⁷ See: The CRISPR revolution: changing life: Conference report. Held on 7 March 2018 <https://royalsociety.org/~media/events/2018/03/crispr-revolution-tof/TOF-crispr-revolution-report.pdf?la=en-GB> and: Tait, J., Banda, G. and Watkins, A. (2017) Proportionate and Adaptive Governance of Innovative Technologies: a framework to guide policy and regulatory decision making. Innogen Institute Report to the British Standards Institution. <https://www.innogen.ac.uk/reports/1222>.

responsible conduct; for example, principal investigators should be role models for their students.

12. Codes of conduct were proposed to be a useful part of a concerted governance system. Some suggested aims were: to raise awareness and broaden discussion; give incentive for assuming responsibility for one's own research; anticipate or pre-empt regulatory requirements; and foster public confidence.

V. Conclusions

13. The workshop session on the way ahead highlighted the importance of continuing discussions on the security implications of genome editing; some of the issues could be developed to expand the scope and scale of further debate. The workshop report indicates the desirability of building on shared evidence and links formed to develop a sustainable network encompassing the scientific and security communities as a basis for extending the engagement more widely. During the workshop, it was pointed out that there would be continuing opportunities for the scientific community to engage with policy makers during meetings of the BTWC. This first Meeting of Experts on the review of developments in the field of science and technology related to the Convention presents such an opportunity - to extend the engagement and draw upon relevant expertise to help us assess the implications of genome editing for the Convention.

**Meeting of the States Parties to the Convention
on the Prohibition of the Development,
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31 July 2018

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2018 Meeting
Geneva, 4-7 December 2018

**Meeting of Experts on Review of developments in the field
of science and technology related to the Convention**
Geneva, 9-10 August 2018

Item 4 of the provisional agenda

**Review of science and technology developments relevant to the Convention,
including for the enhanced implementation of all articles of the Convention
as well as the identification of potential benefits and risks of new science and
technology developments relevant to the Convention, with a particular attention
to positive implications**

**Recent Advances in Gene Editing and Synthesis
Technologies and their Implications**

Submitted by the United States of America

Summary

This paper considers several emerging biotechnology capabilities that may have implications for the Biological Weapons Convention (BWC), in view of their "dual use" implications for bioweapons development. It includes sections on: Gene editing; Metabolic pathway engineering; Gene drives; and Gene synthesis. The paper briefly describes some of the legitimate applications and benefits of these technologies, identifies challenges to realizing these benefits, and describes the nature and impact of their potential BW applications, to permit a balanced assessment. It then describes a recently developed framework for evaluating risks of misuse and identifying mitigation options. Finally, the paper highlights the need for greater international collaboration and harmonization of approaches to address potential biosecurity threats that might result from applications of biotechnology.



I. Introduction

1. Advances in biotechnology, including the ability to engineer genomes of living organisms, bring many benefits to medicine, agriculture, industry, and the environment. At the same time, however, certain advances could expand the range of ways that biology could be used for harm. Biotechnology progress may, in some instances, challenge abilities to develop mechanisms to prevent or mitigate the risks of intentional misuse. Certain recent advances and their actual or potential applications have received a significant amount of attention, both positive and negative— but this attention has not always contributed to a nuanced and balanced understanding of either the potential or the limitations of these advances, nor to a similar understanding of their potential for misuse.

2. The August 2018 BWC experts meeting on advances in science and technology offers a timely opportunity to discuss emerging biotechnologies and consider potential risks, as well as explore foreseeable societal benefits. In some instances, advances in biological sciences may even facilitate the development of countermeasures that mitigate such risks or protect against biological threats. The goal for this analysis is to identify advances of particular concern to the BWC community, and to suggest approaches for future efforts to ensure that beneficial applications of biotechnology can continue to be used safely in medicine, agriculture, industry, and the environment by identifying and addressing risks of potential misuse.

II. Discussion of dual use biotechnology advances and related security concerns

Gene editing

3. Humans have manipulated the genes of natural organisms for thousands of years through intentional and unintentional artificial selection, including selecting for characteristics designed to increase food production of agriculturally important animals, crops, bacteria, yeast, and fungi. Improved understanding of the underlying mechanisms of heredity and the advent of chemical and radiation-based mutagenesis approaches in the early 20th century, followed by the development of recombinant DNA technology in the 1970's, enabled more targeted genetic manipulation of a wide variety of organisms.

4. Newer gene editing tools (including the CRISPR/Cas technology, and others that will continue to be developed) could enable a level of targeted and efficient genomic manipulation not possible previously. At this time, CRISPR-based tools offer greater precision; allow for multiple simultaneous gene edits as well as changing a single letter of genetic code; and are relatively inexpensive, available commercially, and straightforward to use by technical experts¹. These gene-editing tools could benefit agriculture and the environment; for example, by increasing the ability of microbes to fix nitrogen, which would reduce environmental impacts of chemical fertilizer application²; by strengthening disease resistance in both crops and livestock, thereby reducing the application of pesticides; and by increasing desirable traits for sustainable food production and environmental resiliency. The U.S. Department of Agriculture recently approved an oilseed crop and a soybean variety for growth in the United States; both had been edited using CRISPR to produce more omega-3 oil and to be tolerant to drought, respectively.

5. In the health sector, clinical trials are already planned to use CRISPR to correct beta thalassemia and sickle cell disease, both inherited blood disorders caused by a mutation in a

¹ Thurtle-Schmidt, D. M., and Lo, T. W. Molecular biology at the cutting edge: A review on CRISPR/CAS9 gene editing for undergraduates. *Biochem Mol. Biol. Educ.*, 46: 195-205 (2018).

² www.press.bayer.com/baynews/baynews.nsf/id/Bayer-Ginkgo-Bioworks-forces-sustainable-agriculture-forming-company-USD-million-Series-A

gene that makes hemoglobin. Chimeric antigen receptor (CAR) T cell therapy, a potentially remarkable new treatment that uses a person's own immune system to attack cancer cells, is also in development using CRISPR instead of viral vectors³. CRISPR-based and other newer gene editing tools can be used to selectively and reversibly "turn on" or "turn off" genes without changing the genetic code, significantly expanding the range of possible uses of this technology. Moreover, CRISPR technology could allow researchers to more readily modify not only adult ("somatic") cells, but to alter the DNA of heritable ("germline") cells – that is, to make genetic changes that will be passed on to offspring. This raises the possibility of potentially eradicating certain hereditary illnesses in animals or even humans, but also raises a number of important ethical and other considerations that are actively being discussed by the international scientific community, ethicists, and others.

6. Despite the many potential benefits of advanced biotechnologies, CRISPR/Cas and other gene editing tools could be intentionally misused for harmful applications, and thus could be an enabler for bioweapons development. For example, gene editing could be used to manipulate biological agents already of concern to the BWC. Historically, some bioweapons programs focused on altering naturally occurring pathogens to make them deadlier, make them spread more rapidly or easily, or to evade diagnosis and treatment – employing older gene editing tools and well-established recombinant DNA protocols. Newer gene editing approaches could be used for these same goals, arguably with fewer technical challenges than older approaches. Nevertheless, ensuring agent stability, achieving large scale agent production, and finding efficacious means of delivery remain the most challenging aspects of bioweapons development, regardless of the technology used to produce the agent, including by genetic manipulation. By itself, therefore, progress in gene editing may have a limited impact on the overall BW risk. The parallel development and convergence of other technologies (such as nanotechnology and automation) with genetic engineering approaches could lower barriers to weaponization by easing production and delivery challenges, and consequently increase the risk of misuse of gene editing.

Metabolic pathway engineering (a specific case of gene editing)

7. It is now possible to perform "metabolic pathway engineering"—that is, to genetically edit or introduce a novel mechanism into a microbe's internal metabolic production machinery. The creation of such cellular factories is a primary driver of synthetic biological manufacturing, a growing industry devoted to engineering organisms to create a variety of desired molecules in a more sustainable fashion, from biofuels to pharmaceuticals. Metabolic pathway engineering—even when using CRISPR/Cas technology—is technically challenging, and requires sophisticated tools for rational design and complex computation; however, advancement of genetic engineering tools and increasing accessibility also pose dual use concerns by lowering technical barriers and potentially enabling the creation of platforms to produce drugs, toxins, or other chemicals that could be misused or designed to escape traditional regulations for such commodities and their traditional production routes. Researchers have demonstrated the biological fermentation of opioids⁴ and production of a marine conotoxin in the bacteria *Escherichia coli*⁵, for example.

8. A small number of organisms have well-studied cellular pathways (for example, yeast and *E. coli*), but the list is likely to grow. Thus, the numbers of potential biological threat agents could expand and further complicate preparedness efforts and the ability to

³ Eyquem, J., et al. Targeting a CAR to the TRAC locus with CRISPR/Cas9 enhances tumour rejection. *Nature*, 543: 113-117 (2017).

⁴ Galanie, S., et al. Complete biosynthesis of opioids in yeast. *Science*, 349: 1095-1100 (2015).

⁵ Zhu, X., et al. Recombinant Expression and Characterization of α -Conotoxin LvIA in *Escherichia coli*. *Marine Drugs*, 14: 11 (2016).

mitigate public health concerns, or make the production of certain toxins cheaper and easier.

Gene drives (a specific application of biotechnology)

9. A gene drive is a way to “drive,” or push, the prevalence of a gene in a sexually reproducing population so that a biased proportion of offspring will inherit a gene(s) of interest (in theory, close to 100% of offspring). There are many examples of gene drives that occur in nature (e.g., meiotic drives), but an *engineered* gene drive could make the addition, disruption, alteration, or suppression of specific genes within a target population of organisms a reality. As they require sexual reproduction and rapid life cycles to propagate, engineered gene drives would theoretically work best in insects and other organisms with short generation times and large numbers of offspring. Some proposed beneficial uses of engineered gene drives include eliminating disease transmission by mosquitoes, engineering crop pests to remove their resistance to pesticides, or making certain populations of invasive species like mice and other rodents infertile.

10. Resistance mechanisms to gene drives have been found⁶, so the effectiveness of engineered gene drives for beneficial or malign purposes could be more complicated and less complete in a target population than previously thought. Also, gene drives are only relevant in species with sexual reproduction, so they could not be engineered to affect viruses and bacteria. While gene drives could, in theory, be used to alter human populations, the long generation time would make this an extremely long-term and unlikely proposition. In spite of these limitations, engineered gene drives hold dual use implications, as well as biosafety and biosecurity concerns. For example, engineered gene drive technology might be used to develop insects to intentionally spread diseases such as Zika or Dengue. The technology could also be used to alter populations of weeds or pests that harm crops or livestock by actors intent on harming food supplies.

11. It is key to note, however, that field trials of modified organisms containing an engineered gene drive have not yet occurred. Models have predicted a range of outcomes⁷, from the evolution of resistance (ineffective drive) to effective drives that could have either intended or unintended consequences. Therefore, appropriate biosafety or biosecurity precautions should be followed to minimize the risks of such unintended consequences to the environment, as well as plant, animal, and human health. Notably, many of the potential environmental impacts of engineered gene drives are already being addressed by international fora other than the BWC.

Gene synthesis

12. The ability to synthesize DNA has become commonplace in both industrial and academic laboratories all over the world. The chemical synthesis of DNA oligonucleotides and their subsequent assembly into genes, pathways, and even entire genomes by synthetic biology methods has enabled biomedical research. DNA synthesis also enables the “design, build, test, and learn” cycle that underpins innovations in energy, agricultural, and health sectors. For example, the ability to produce vanilla from genetically modified yeast – rather than harvest the pure extract from vanilla beans – provides a cost-effective

⁶ Champer, J., et al. Novel CRISPR/Cas9 gene drive constructs reveal insights into mechanisms of resistance allele formation and drive efficiency in genetically diverse populations. *PLoS Genet.*, 13: e1006796 (2017).

⁷ Tanaka, H., Stone, H. A., and Nelson, D. R., Spatial gene drives and pushed genetic waves. *Proc. Natl. Acad. Sci. USA*, 114: 8452-8457 (2017); Eckhoff, P. A., et al. Impact of mosquito gene drive on malaria elimination in a computational model with explicit spatial and temporal dynamics. *Proc. Natl. Acad. Sci. USA*, 114: E255-E264 (2017); Turelli, M., and Barton, N. H., Deploying dengue-suppressing Wolbachia: Robust models predict slow but effective spatial spread in *Aedes aegypti*, *Theor. Popul. Biol.*, 115: 45-60 (2017).

alternative with potentially lower environmental impact from unsustainable farming practices. Synthetic insulin, used by millions of diabetics, is made in both bacteria and yeast from DNA building blocks.

13. With decreasing costs to synthesize DNA, along with increasing demand for high fidelity DNA sequences, the gene synthesis industry has grown from a small handful of companies just a decade ago, to a marketplace of dozens of companies around the world, as well as into the hands of independent laboratories. The lengths of sequences that can be synthesized has continued to grow; the cost and time have continued to drop; and companies increasingly offer design services or tools to facilitate design (e.g., by optimizing expression of a given gene for the system in which it is to be inserted). Gene synthesis could therefore facilitate the creation of harmful biological agents "from scratch," produced outside of industry and other controlled commercial pipelines.

14. Although synthesizing genes is relatively straightforward, it is important not to overstate the ease of combining genetic elements to re-create harmful organisms *de novo*, as it is quite complicated; the level of difficulty is proportional to the size/length of the genomic DNA needed, and the overall complexity of the organism. There are also two steps required: the organism's genome must be synthesized in pieces and assembled, and then converted into a functioning biological organism, known as "booting." Re-creation and booting of a bacterial cell, although it has been accomplished⁸, remains extremely technically challenging and, in many instances, expensive – and the recreation of eukaryotic organisms, such as yeast and fungi are, at present, not possible. However, synthesizing the genome of almost any mammalian virus is now possible, and sequences of most known human viruses are available on public internet databases such as GenBank, an annotated collection of all publicly available DNA sequences.

15. Experiments of this kind have already been performed, including the synthesis of polio virus and, more recently, the re-creation of the 1918 influenza virus⁹ and the horsepox virus¹⁰. The publication of the smallpox virus genetic sequence in 1994¹¹; creation of a bacterial cell with a synthesized genome in 2010¹²; and the synthesis and booting up of multiple viruses, including polio virus in 2002¹³, a bacteriophage in 2003¹⁴, and the 1918 influenza virus in 2005⁹, were all legitimate research efforts. Although the creation and booting of some viruses (e.g., polio) has been achieved using cell-free extracts, most viruses must be booted inside cells, which requires additional time and technical expertise. Furthermore, some viruses, including horsepox virus, require the use of additional helper viruses and other specialized molecular tools, requiring considerable technical expertise, experience, and knowledge¹⁵. Synthesizing certain bacteria and toxins is also possible, although to a lesser extent than viruses, for several reasons both technical and scientific.

16. The capability to chemically synthesize or genetically engineer viruses poses biosecurity risks and should serve as a strategic warning to BWC States Parties that

⁸ Hutchison, C. A., 3rd, et al. Design and synthesis of a minimal bacterial genome. *Science*, 351: aad6253 (2016).

⁹ Tumpey, T. M., et al. Characterization of the reconstructed 1918 Spanish influenza pandemic virus. *Science*, 310: 77-80 (2005).

¹⁰ Noyce, R. S., Lederman, S., and Evans, D. H. Construction of an infectious horsepox virus vaccine from chemically synthesized DNA fragments. *PLoS ONE*, 13: e0188453 (2018).

¹¹ Massung, R. F., et al. Analysis of the complete genome of smallpox variola major virus strain Bangladesh-1975. *Virology*, 201: 215-240 (1994).

¹² Gibson, D. G., et al. Creation of a bacterial cell controlled by a chemically synthesized genome. *Science*, 329: 52-56 (2010).

¹³ Cello, J., Paul, A. V., and Wimmer, E. Chemical synthesis of poliovirus cDNA: generation of infectious virus in the absence of natural template. *Science*, 297: 1016-1018 (2002).

¹⁴ Smith, H. O., et al. Generating a synthetic genome by whole genome assembly: phiX174 bacteriophage from synthetic oligonucleotides. *Proc. Natl. Acad. Sci. USA*, 100: 15440-15445 (2003).

¹⁵ DiEuliis, D., Berger, K., and Gronvall, G. K. *Health Security*, vol. 15 (Dec 2017).

biosecurity controls and preparedness – that rely primarily on controlling access to dangerous, existing pathogens – may be insufficient¹⁶. While many gene synthesis providers screen customers and orders for biosecurity concerns, following the recommendations of the industry-led International Gene Synthesis Consortium (IGSC) and/or the U.S. Department of Health and Human Services' *Screening Framework Guidance for Providers of Synthetic Double-Stranded DNA*¹⁷, such practices are not universal. Given that gene synthesis is performed by an array of international companies, and benefits legitimate research in many BWC State Parties, achieving greater safety and security around it will require discussions at international fora¹⁸. For example, dual use experiments which involve the creation of viruses for public health benefits (e.g., for the CAR T cell therapies mentioned above, or for vaccines) should be carefully reviewed for their risks, benefits, and safety – yet there is currently no broadly accepted set of norms for assessing risks and benefits of these experiments.

III. Science-based risk/benefit assessment as a tool for evaluating dual use capabilities

17. New biotechnology tools are benefiting human, agricultural, and environmental health, but also expanding capabilities for potential bioweapons development. As many scenarios are *possible*, it has been a difficult challenge for policy makers and regulators to focus on what might be *probable* or even feasible in a bioweapons context. In response to this problem, the United States government commissioned the U.S. National Academies of Sciences, Engineering, and Medicine to develop a framework for systematically evaluating the security implications of synthetic biology¹⁹. The Academy's study framework is focused on emerging, modern capabilities in biological engineering and is widely applicable. Factors for assessing the capability for malicious use of a biotechnology can include:

- The nature and capability of the technology itself;
- Its potential use as a weapon; i.e., how feasibly it could be weaponized, and its scope of damage or impact; and
- The attributes of actors who could command such a capability, including expertise, resources, and organizational footprint.

18. These factors must be weighed against the factors available for mitigation, which include:

- Deterrence and prevention of misuse;
- The ability to recognize a bioweapons attack has occurred;
- The ability to attribute an attack to the perpetrator; and
- The ability to provide for consequence management and recovery.

19. For example, while a particular agent may be possible to create in the laboratory it may be very difficult to deliver. Or, an agent to be re-created and delivered may already have a medical countermeasure available, possibly acting as a deterrent.

¹⁶ DiEuliis, D., Gronvall, G. K. A holistic assessment of the risks and benefits of the synthesis of horsepox virus. *mSphere*, 3: e00074-18 (2018).

¹⁷ www.phe.gov/Preparedness/legal/guidance/syndna/Pages/default.aspx

¹⁸ DiEuliis, D., Carter, S. R., Gronvall, G. K. Options for synthetic DNA order screening, revisited. *mSphere*, 2: e00319-17 (2017).

¹⁹ National Academies of Sciences, Engineering, and Medicine. *Biodefense in the Age of Synthetic Biology*. Washington, DC: The National Academies Press (2018). <https://doi.org/10.17226/24890>.

20. Importantly, these factors are related to risk analysis – or, in the least, generating a level of concern for particular scenarios enabled by emerging biotechnology. Overall, these concerns should be weighed against the potential benefits proposed by the research. Balancing risks and benefits can be a fraught process, as exemplified by recent controversy surrounding “gain of function” avian influenza research. As a subset of research in areas where there is potential for misuse, gain of function research is being defined in this context as experimentation that could increase the transmissibility and/or virulence of pathogens. Thus, the benefits to pandemic preparedness (prediction, surveillance, detection, and treatment) must be weighed against the risk of creating potential pandemic agents in the process that could be used for harm, or unintentionally released. A summary of such discussions can inform the risk/benefit analysis process²⁰.

IV. Converging international approaches for ensuring safe and secure use of emerging biotechnologies

21. Perhaps not surprisingly, scientific and technological advances in recent years in the biosciences have been accompanied by concerns about the possible misuse of research results for malign applications. Preventing deliberate misuse of these advances in the biological sciences is, of course, a key aim for the BWC States Parties. Vigorous discussions are taking place in the scientific community and government in the United States and in other international and domestic fora to assess the risks of emerging biotechnologies and to develop mechanisms for preventing or mitigating misuse while, importantly, not hindering legitimate research and beneficial applications.

22. For example, the Interacademy Partnership (IAP), representing more than 130 national and regional member academies of science, sponsored a workshop in October 2017 entitled “Assessing the Security Implications of Genome Editing Technology”²¹. While international discussions are still at an early stage, the IAP identified a number of key messages from the workshop:

- Recent evidence confirms that genome editing will be an important tool to drive innovation in pursuit of societal priorities.
- As with other tools, it could be misused, inadvertently or deliberately. While the advantages of genome editing lead to its widespread use, this does not in itself directly promote intent to misuse. There must be balanced discussion about benefit and risk, valuing benefits in ways that are relevant to the public. Benefits may include increasing security for human health and agriculture.
- [The] workshop discussions represent significant progress in bringing together members of the science, security and policy communities to clarify if, where and how intentional misuse can be expected and what we might do to prepare for and mitigate such eventualities. We must listen to concerns about misuse while also making clear what is, or is not, scientifically feasible. We must continue building a culture of research responsibility and integrity, knowing that uncertainty may undermine public confidence in science and that other stakeholders may have different expectations of evidence.
- The voices of our countries worldwide are essential in our collective efforts to assess value and harmonize procedures for risk assessment and management. It is highly desirable to build on the evidence shared and the links formed in [the] workshop to develop a sustainable network encompassing the scientific and

²⁰ Institute of Medicine and National Research Council. *Potential Risks and Benefits of Gain-of-Function Research: Summary of a Workshop*. Washington, DC: The National Academies Press (2015). <https://doi.org/10.17226/21666>.

²¹ www.interacademies.org/43251/Assessing-the-Security-Implications-of-Genome-Editing-Technology-Report-of-an-international-workshop

security communities as a basis for extending the engagement more widely. IAP is ready to continue playing its part in doing this.

23. The United States considers that the issue of potential misuse of biotechnological advances is not unique to advances in gene editing. For example, gain-of-function influenza research may make use of advanced gene editing techniques, or may use simpler expedients, such as serial passage through numerous animal specimens, as a means of acquiring a desired trait. The United States government has developed guidelines governing research that may be considered gain-of-function (now "potential pandemic pathogen care and oversight"²²). In addition, the United States government has policies on the oversight of "dual use research of concern" (DURC)²³, which seek to preserve the benefits of life sciences research while minimizing the risk of misuse of such knowledge or technologies. A number of other countries have developed similar guidelines. The United States welcomes international discussions in the BWC and elsewhere, and looks forward to continuing to play an active part in further international efforts at sharing and harmonizing best practices and norms around biosecurity.

24. In addition to deliberate misuse of advances in the biosciences, safety mishaps, inadvertent misuse, or negligence could also lead to unintended consequences. In some scenarios, safety failures might even lead to a Public Health Emergency of International Concern (PHEIC), as defined by the World Health Organization. When such a disease event is first detected and reported, it may also be difficult to determine whether the potential PHEIC is the result of deliberate misuse, a natural emergence, or an accident.

V. Conclusion

25. To ensure that countries continue to apply advances in biotechnologies for peaceful purposes and, in turn, reap the undoubted benefits that these technologies otherwise afford, there is a need for countries to develop and implement biosafety and biosecurity policies and approaches, and to share these internationally among BWC States Parties. The development of measures for ensuring safety and security of biological laboratories, as well as for preventing or mitigating intentional or unintentional misuse of biotechnology, is traditionally a national matter. Nations have their own laws and regulations regarding handling and protection of pathogens, and preventing misuse of research findings. Given increasing international research collaborations and the potential global consequences of misuse of advances in the biosciences, it is desirable to discuss and find ways to harmonize national practices. Examples of successful harmonization and international adoption of biosecurity policies include - together - the approaches to managing gene synthesis risks taken by the U.S. Department of Health and Human Services' *Screening Framework Guidance for Providers of Synthetic Double-Stranded DNA*, the IGSC, and the Australia Group. Continuing and expanding such efforts will require close cooperation between the BWC States Parties and the international scientific community.

²² www.phe.gov/s3/dualuse/Pages/p3co.aspx

²³ <https://osp.od.nih.gov/biotechnology/dual-use-research-of-concern/>

**Meeting of the States Parties to the Convention
on the Prohibition of the Development,
Production and Stockpiling of Bacteriological
(Biological) and Toxin Weapons and on Their
Destruction**

6 August 2018

English only

2018 Meeting
Geneva, 4-7 December 2018

Meeting of Experts on Review of developments in the field
of science and technology related to the Convention

Geneva, 9-10 August 2018

Item 7 of the provisional agenda

Genome editing, taking into consideration, as appropriate,
the issues identified above

**Review of Developments in the Field of Science
and Technology Related to the Convention -
Genome Editing**

Submitted by the Islamic Republic of Iran

1. Many biological scientists view the present century as the century of genetic engineering and molecular biotechnology. By applying gene engineering, scientists strengthen or modify the inherited characteristics of living organism. Relying on new genetic engineering methods, biotechnology in the last three decades has offered and demonstrated diverse and valuable capabilities in various fields of science. Genome editing is one of the few cases in which fundamental researches have quickly reached an applied level. Genome editing technology today has widespread applications for peaceful use in various fields including in medical sciences, industry and agriculture.

2. The discovery of main genes inducing diseases, the use of various genetic screening methods and accurate predictions about fetal fate determination with respect to genetic diseases before and after birth are among notable capabilities of genetic engineering and gene therapy. Despite the fact that gene therapy is currently costly and requires advanced and specialized techniques, however, this method will soon be used for a wide range of diseases. There is also growing and promising evidence that use of modern methods in the not-so-distant future will reduce the cost of treatment hundreds of times.

3. The genetic engineering applications in medical and pharmaceutical sciences includes, among other things, the invention of new methods for molecular diagnosis of pathogenic mechanism, the production of new drugs and recombinant vaccines, the development of diagnostic kits, the production of monoclonal antibodies, and so on. As an example, human insulin is now produced as a recombinant protein which is very similar to

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human insulin and its production is inexpensive which makes it possible to use for patients in developing countries.

4. Efforts to treat cancer with the use of genetic engineering and molecular biotechnology are being intensified. Among various genome editing technologies, Clustered, Regularly Interspaced, Short Palindromic Repeat (CRISPR) technique is the most attractive one and has been widely used for its effectiveness, precision and low cost. This technique is being applied in the treatment of serious diseases such as cancers and production of new drugs and vaccines and for other peaceful purposes. The overwhelming majority of genetic scientists with the understanding of their responsibility believe that their efforts and researches in the field of genetic engineering and molecular biotechnology can lead to very valuable applications in medical fields which should be used only for the purposes of prevention, diagnosis and treatment of diseases.

5. Genetic engineering has various applications in the industry and provides valuable contribution in the industrial production of required materials for food industry and cleaning products. The design of genetically engineered microbial strains has led to major advances in the production of enzymes and biocatalyst as the main materials in various food, chemical, cellulose, oil, detergent industries and so on. Industrial production of many organic acids such as citric acid, acetic acid and lactic acid, as well as the production of oils with special fatty acid compounds which have high value in food industry and cleaning products and also the production of protein polymers are examples of active genetic engineering presence and applications in the industry. Genome editing technology, in particular CRISPR is used in the industry for targeted manipulation and increased efficiency. Recently, a group of scientists, using CRISPR technology, succeeded in modifying and genetically engineering algae. As a result, reportedly the production of biofuels based on algae has more than doubled.

6. The growing world population underlines the need to and importance of sufficient food supply and food security. Genetic engineering could contribute directly and indirectly to food security through enabling mass production and provision of biological pest control. It is expected that the genome editing would play a significant role in the human efforts in this regard.

7. Applications of genome editing technology in medical, pharmaceutical, industrial and agricultural fields have brought economic growths and financial profits for the countries which possess such a capability. The global market for products and services based on genome editing technique is expected to substantially increase. In some countries the number of patent applications in the field of gene editing has significantly increased in recent years. Currently, a limited number of countries have acquired the capability of applying genome editing technology not only for their scientific research and the promotion of the public health, but also for contributing to their economic growth.

8. States Parties to the Biological Weapon Convention (BWC) have undertaken, under Article X, to facilitate "the fullest possible exchange of equipment, materials and scientific and technological information for the use of bacteriological (biological) agents and toxins for peaceful purposes." They have the inalienable right to participate in such an exchange. "Parties to the Convention in a position to do so shall also co-operate in contributing individually or together with other States or international organisations to the further development and application of scientific discoveries in the field of bacteriology (biology) for the prevention of disease, or for other peaceful purposes." Furthermore, Article X articulates that "this Convention shall be implemented in a manner designed to avoid hampering the economic or technological development of States Parties to the Convention or international co-operation in the field of peaceful bacteriological (biological) activities."

9. States Parties to the BWC in particular developed countries and those possessing advanced biotechnology have legal commitment, under Article X of the BWC, to cooperate

in capacity building, knowledge sharing and transfer of technology in the areas of preparedness, prevention, protection, diagnosis and treatment and other peaceful purposes. Given the wide range of applications of genome editing for peaceful purposes and the gap between developed and developing States Parties in enjoying the benefits of this technology, provision of international cooperation in particular for knowledge sharing and transfer of technology in the area of genome editing is essential for capacity building in developing States Parties and reducing the existing gap between developed and developing States Parties.

10. Applying restrictive measures by certain States to cooperation with States Parties including imposition and maintenance of restrictions and limitations in exchange and transfer of knowledge, technology, equipment and materials associated with new technologies such as genome editing and CRISPR technique for peaceful purposes are unjustified and inconsistent with the provisions of the BWC in particular Article X obligations. Various applications of genome editing in the fields of health, diagnosis and treatment of disease as well as in the area of production of industrial products underlines the importance and necessity of access to this technology and relevant knowledge for developing countries.

11. While concerns regarding potential risks of genome editing need to be addressed appropriately including by redoubling efforts to enhance universalization of the BWC, such concerns should not be used as a pretext to hamper the economic or technological development of States Parties to the Convention or international co-operation in the field of peaceful biological activities and to deprive developing countries from access to genome editing technology and its benefits.

12. Considering the above-mentioned points, the Islamic Republic of Iran believes that the one-sided view of some developed countries towards potential risks of genome editing continues to hinder the access of developing countries to such an important technology. Such an approach is wholly inconsistent with the objectives of the Convention and the 2018 Meeting of Experts on review of developments in the field of science and technology related to the Convention should reach to common understandings regarding facilitation of cooperation in the area of genome editing among States Parties with a view to agreeing on effective action in this regards, in accordance with its mandate.